



The Role of Signaling Pathway on Osteoprogenitor Cell Behavior and Bone Formation

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Abstract

Different biomarkers and signaling pathways are involved in bone development. These factors lead to different osteoprogenitor cell reactions. Proliferation, migration, and differentiation of osteoprogenitor cells is induced by different intracellular and extracellular molecular signaling pathways. As mesenchymal stem cells (MSCs) and their differentiation during repair and development of bone processes have significant roles, it is believed that sensible molecular signaling pathways involvement is vital to the development of bone formation, bone substitute materials, and bone repair. This study reviews various keys of signaling pathway that terminate proliferation, migration, and differentiation of osteoprogenitor cells.

Keywords: Bone, Signaling Pathways, Osteoprogenitor, Proliferation, Differentiation

1. Context

Mesenchyme and stem cell have particular actions and function, such as proliferation, migration, and differentiation, independent of signaling pathways, biomarkers and etc. Researchers for the first time showed an origin of human mesenchyme stem cells, which is from the perivascular area (1-3). Furthermore, HMSC with special cluster of differentiation, such as CD₃₇, CD₉₀, and CD₄₀ with little increased expression of CD₁₄, CD₃₄, CD₄₅, and human leucocyte-DR (HLA-DR) can differentiate to osteoblast cells (4). Researchers exploit HMSC from different sources, such as dental tissue, endometria menstrual, blood, peripheral blood, placenta and fetal membrane salivary gland, skin, synovial fluid, foreskin, endometrium amniotic fluid, sub-amniotic umbilical cord lining membrane, and Wharton jelly (5).

Different types of bone cells have a significant effect in development and formation of bone (mineralization and matrix).

During life, bone is remodeled and osteoblast cells differentiate from mesenchyme progenitor cells that proliferate migration and differentiation, which depends on

balancing at bone mass and function (3). Good performance of osteoblast cells is required in the maintenance of regular bone homeostasis. This evolution is coordinated by multiple extracellular signals that are transduced by cell signaling pathways to monitor specialized changes in gene expression

Bone, as a specialized form of connective tissue, is the main component of the skeletal system. Bone formation is very complex and is controlled by multiple signaling factors that play a major role in the regulation of osteoblast and other bone lineage-specific differentiation (4, 5).

2. Evidence Acquisition

2.1. Effect of Ras-MAPK-Pathway on Osteoprogenitor Cells

Receptor tyrosine kinase, as a signaling pathway, has a key role in the development of osteoprogenitor cells.

Ras facilitates activation of mitogen activation protein kinase (MAPK), (phosphatidylinositol, tol 3'-kinase) PI3K and insulin-like growth factors (IGFs) by loss of the NF1 gene (6-8).

Ras-MAPK-pathway in osteoblast progress regulates EPK signaling to form the skeletal structure. Most times,

EPK facilitates differentiation of osteoprogenitor cells without changing proliferation (9).

The PI3K pathway as well as EPK plays a key role in osteoprogenitor for proliferation, by inhibition of EPK signaling pathway (10).

FGFR3 has a negative regulation on function and proliferation of osteoprogenitor cells, and inhibits IHH signaling pathway to maintain PTHLH expression in reserve and articular chondrocyte (11).

2.2. Effect of BMP/TGF- β s Pathway on Osteogenic Cells

The transforming growth factor- β (TGF- β) superfamily is comprised of TGF- β s, activin, bone morphogenetic proteins (BMPs), and other related proteins. TGF- β acts through the heteromeric receptor complex, comprised of type I and type II receptors at the cell surface that transduces intracellular signals by Smad complex or MAPK cascade (12-17). At least 29 and probably up to 42 TGF- β , five type II receptors and seven type I receptors are encoded by the human genome (18, 19). Signals transduced by TGF- β superfamily members control the formation of tissue differentiation, through their effects on cell proliferation, differentiation, and migration (20-23).

Change of BMP and TGF- β as key factors of formation and development of osteoprogenitor cells leads to bone disorders, such as osteoarthritis, brachydactyl type A2, and tumor metastasis (24).

Furthermore, BMP activates Smad 1 and 5, as extracellular signals. TGF- β signaling pathway regulates proliferation, differentiation, and bone formation by activation of Smad2, 3. The MAPK cascade is involved in significant cellular action, such as movement, division, death and cell differentiation. To regenerate bone, P₃₈/MAPK signaling activation has a significant effect for induction of osteoblast differentiation (25-32).

2.3. Effect of Ca²⁺ Signaling Pathway on Osteogenic Cells

Ca²⁺, as a significant factor in osteoprogenitor cells, differentiates to osteoblast and regulates Runx 2. Furthermore, Runx 2 signaling pathway regulates ATP-dependent Ca²⁺ influx through calcium channels (33).

AP-1 is up-regulated by high levels of Ca²⁺ intracellular and leads to activation of growth factors, such as IGF1/2, VEGF, TGF- β , and BMP, and these factors cause high osteoblastic function and enhancement of mineralization capacity of osteoprogenitor cells. It has been established that Ca²⁺ results in significant enhancement of the proliferation level of hPDCs and MC3T3 and morphology alteration from fibroblastic to cuboidal, which is a prominent normal function of osteoblasts. On the other hand, revelation of the influence of Ca²⁺ signaling may also be profitable in the explanation of how CaP biomaterials can rise

osteoblastic activation and high mineralization capacity of osteoprogenitor cells (34-37). The Ca²⁺ channels are activated by CaP crystals, which leads to high expression levels of the bone sialoprotein, osteopontin, and ALP (38). Furthermore, upon treatment of hMSCs with elevated Ca²⁺, enhancement in proliferation rate and expression of bone related genes, such as osteocalcin, bone sialoprotein and osteopontin, as well as BMP-2 was observed, indicating that Ca²⁺ is a potential osteoinductive trigger in hMSCs by interacting with the BMP2 signaling pathway (39).

2.4. Effect of Wnt Active Wnt/ β Catenin Signaling Pathway on Osteogenic Cells

Wnt, as a large family of ligands, for membrane-spooning frizzled (FZD) receptors, is involved in proliferation, growth, migration, polarity, differentiation, and cell death (40, 41). Wnt/Ca²⁺ and Wnt/planer facilitate osteoblast differentiation and mineralization processes. Wnt30 enhances proliferation of osteoprogenitor cells. Wnt-responding cells, which undergo a transient step of cell differentiation induced by local Wnt stimuli, regulate bone formation (42-44).

2.5. Effect of IGF Signaling Pathway on Osteogenic Cells

These significant members of IGF, IGF1 and IGF2, are involved in proliferation and differentiation of osteoblast (45). IGF2 is the growth factor that is responsible for osteoblast differentiation. However, in contrast to IGF1, IGF2 modulates and maintains bone mass. Both IGFs are expressed in osteoblasts and have similar biological function and properties (46, 47). Induction of osteoblast differentiation, stimulation of bone matrix deposition, expression of collagens, and non-collagenous proteins are among various effects of IGF1 and IGF2 in bone (48). Additionally, IGF-1 in combination with BMP2 has a stimulatory impression on the proliferation and osteogenic differentiation of stem cells derived from adipose tissue (49).

2.6. Effect of Panx3 Signaling Pathway on Osteoprogenitor Cells

Pannexins (Panxs) were recently recognized as a new gap junction protein family (50, 51). The Panx family consists of three members, Panx1, 2, and 3. Panx1 and 2 are ubiquitously expressed with particularly strong expression in the central nervous system (52). Panx3 is a member that was most recently identified by genome bioinformatic analysis (53). However, Panx 3 is expressed in certain soft tissues, such as skin and coronary arteries and developing hard tissues, including cartilage and bone. Panx3 has a negative impression on regulation proliferation and differentiation of osteoprogenitor cells. Panx signaling pathway inhibits proliferation by deduction of expression of cAMP/plcA signaling (54, 55).

3. Results

In summary, review of the literature indicates that a signaling pathway regulates proliferation, migration, differentiation of osteoprogenitor cells to osteoblast and bone formation. The current results indicated that different signaling pathways and different stages of cells have different actions.

4. Conclusions

This study reviewed how natural fracture restoration and regeneration take place following bone injuries. The different signal pathways in bone formation by MSCs have been discussed. Finally, this research discussed specifications and the involvement of diverse key molecular signaling pathways in special bone cells development. The current authors believe that a deeper understanding of the molecular signaling pathways involved in bone formation and structure can help bring novel therapies from the bench to the bedside in bone injury.

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Footnotes

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